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DOI: https://doi.org/10.1007/s15010-013-0578-9

FIRST DOCUMENTED OUTBREAK OF KPC-2 PRODUCING *K. PNEUMONIAE* IN SWITZERLAND: INFECTION CONTROL MEASURES AND CLINICAL MANAGEMENT

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EL and PK contributed equally to the work. All authors have seen and approved the manuscript.

The manuscript has not been published and is not being considered for publication elsewhere.

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Abstract

We report the epidemiological and clinical features of the first outbreak of KPC producing *Klebsiella pneumoniae* (KPC-KP) type 2 in Switzerland. The outbreak took place in the medical ICU of our tertiary care hospital and affected three severely ill patients. After implementation of strict infection control measures, no further colonisations could be detected by screening of exposed patients. Successful treatment consisted of a triple therapy of meropenem, colistin and tigecycline.

Key words: Carbapenem-resistant Enterobacteriaceae (CRE), KPC, *Klebsiella pneumoniae*, outbreak, Switzerland, infection control

Text

Introduction

Within the last decade, carbapenem-resistant Enterobacteriaceae (CRE) have become a major global threat [1,2]. One of the most common CRE, carbapenemase-producing *Klebsiella pneumoniae* (KPC-KP), was first described 1996 in Eastern USA and has since spread globally [2,3]. Prevalence of KPC-KP in Europe is increasing, although rates vary considerably between countries [1]. A north-south gradient can be seen with KPC-KP being endemic in Italy, Greece and Israel [1]. A recent survey from Italy reported several hospital outbreaks and countrywide dissemination of KPC-KP [4,5]. In many European countries with low KPC prevalence, outbreaks have been linked to patients transferred from endemic regions [1,6].

In Switzerland, the prevalence of KPC-KP is unknown, as only data on the number of isolates with elevated minimal inhibitory concentrations (MIC) for carbapenems are available [7]. The first description of a KPC producer was a KPC-2 *K. pneumoniae* isolate in urine and sputum samples from a patient transferred from Sicily (Italy) to Neuchâtel (Switzerland) in 2011 [8]. Subsequently, four unrelated cases of KPC-2 and KPC-3 *K. pneumoniae* were reported from the University Hospital of Basel. All four cases were related to endemic countries [9].

We report the first outbreak of KPC-KP in Switzerland, its epidemiological and clinical features as well as the infection control measures implemented during the outbreak period.

Methods

Setting

Our institution is a 700-bed tertiary care hospital in Eastern Switzerland, treating approximately 33'000 inpatients annually. Supposed transmission of KPC-KP took place in the 12-bed medical intensive care unit (MICU) between February and April 2013. In 2012, a total of 2'108 patients were hospitalized on the ward accounting for 5870 patient-, 1610 ventilation- and 257 dialysis-days. At the time of the outbreak, an admission screening only for MRSA was performed for patients at risk [10].

Microbiology

Aerobic and anaerobic blood cultures were incubated in the Bactec™ FX (BDBioscience, San Jose, CA) according to the manufacturer instructions. Positive blood cultures and samples of the lower respiratory tract were processed according to standard procedures [11,12].

Since selective culture media for KPC-KP were not available in our laboratory during the outbreak screening was done as follows. Nasal, pharyngeal, rectal, axillary and inguinal screening swabs (Copan, Brescia, Italy) were inoculated on MacConkey agar plates (BD Bioscience, San Jose, CA) for 24 and 48 hours. Growing colonies of different morphotypes were identified by MALDI-TOF (Bruker, Billerica, MA) and susceptibility testing was performed with the BD Phoenix™-100 (BD Bioscience, San Jose, CA) system according to CLSI guidelines [13]. Multiresistant *K. pneumoniae* with elevated MICs for carbapenems were further tested with Etest® containing imipenem (with and without EDTA), double disk synergy test with boronic acid as well as with the modified Hodge test [9,13]. MICs of colistin and tigecycline were

determined with Etest® (BioMérieux, Marcy-l'Etoile, France). KPC-specific conventional polymerase chain reaction (PCR) was followed by direct sequencing as previously described [9]. Molecular typing of KPC-KP was done using PFGE using restriction endonuclease *Xba*I according to Babouee et al. [14], with the exception of calculating percent similarities based on the Pearson instead of the Dice coefficient. PFGE patterns were analysed using software package GelCompar II, version 5.10 (Applied Maths NV, Sint-Martens-Latem, Belgium).

Results

Outbreak description and epidemiological investigation

In case 1, KPC-KP was detected in a blood culture on March 17th. On the same day, case 2 revealed a KPC-KP positive bronchial secretion. Therefore an outbreak investigation according to international guidelines was initiated [15].

As cases 1 and 2 were roommates in the MICU from March 7th to March 11th, this ward was identified as putative place of transmission and screening of patients at risk was performed. Active screening revealed a third patient (case 3) on March 21th with KPC-KP positive screening samples (Fig 1).

All patients hospitalised for more than three days were planned to undergo screening, if they stayed on the MICU between February 19th and April 23th. Screening was repeated every 7 days for patients in the MICU. If patients were discharged from the MICU, two additional screenings 7 days apart were planned.

Case one was also hospitalised on the hemato-oncology ward during the outbreak period. Since he always stayed in a single room and hand hygiene adherence was over 80%, no further screening was done in the hemato-oncology ward.

36 patients were planned to undergo screening. 21 completed the screening with at least two screenings being negative (one patient with 6 screenings, 6 patients with 3 screenings and 14 patients with 2 screenings). 13 patients had incomplete screenings, with 7 patients having only one negative screening and 6 patients having been discharged from our institution before start of screening. Patients with incomplete screening were labelled in our electronic alert system to ensure screening at rehospitalisation. Two patients died. One passed away after unsuccessful

resuscitation following cardiac arrest. The second patient was discharged from the MICU to a rehabilitation clinic after treatment of cardiogenic shock. He was readmitted to another hospital because of hematothorax and died of bronchopneumonia. KPC-KP as the cause of the pneumonia can not be excluded. Both patients were not screened.

Infection control measures and interventions

Cases were put under contact precautions and patient cohorting was initiated. Staff cohorting was arranged but could not be strictly maintained. At time of outbreak detection, all rooms, surfaces and devices were disinfected with a quarternary ammonium-based formulation. This procedure was repeated 3 weeks after outbreak detection. In addition, disinfection was repeated each time an isolated patient was discharged from the MICU. Hand hygiene adherence and hygiene behaviour was observed by infection control specialists and direct feedback was given to the healthcare workers. During the outbreak, hand hygiene adherence according to WHO-guidelines [16] was 82% (243 opportunities observed).

Patients transferred to other units in our institution were not preemptively contact isolated, but health care workers, patients and family members were encouraged to adhere to standard precautions, especially to hand hygiene.

For patients at risk having been discharged from our institution before start of the screening, health care workers involved in subsequent patient care were informed.

Microbiological investigations

The isolated strains from cases 1, 2 and 3 were sent to the reference laboratory in Basel, where phenotypic and molecular methods confirmed KPC-KP. Genotyping after sequencing exhibited betalactamase (*bla*) KPC-2 gene. Additionally, PFGE of the three *K. pneumoniae* strains showed very similar fingerprints indicating clonal identity (Fig 2).

Description of cases (Table 1)

Case 1

Case 1, a 54-year old man with multiple myeloma, was hospitalised on February 25th for administration of high dose chemotherapy. He was transferred to the MICU on March 7th because of aplasia and bilateral pneumonia with persistent fever spikes. After being treated with piperacillin/tazobactam he clinically improved and could be transferred back to the hematoncology unit on March 11th. Three days later the patient again developed fever. Blood cultures from March 17th grew KPC-KP and antibiotic therapy was switched to meropenem and tigecyclin. Assuming catheter-related bloodstream infection, the central line was removed and the catheter tip cultured (no growth). The patient subsequently recovered quickly and antibiotic therapy was stopped on the day of hospital discharge on March 29th. On April 4th however, he had to be readmitted due to pneumonia. KPC-KP was again isolated from the bronchoalveolar lavage (BAL) and meropenem, tigecycline and colistin were administered for 12 days. The patient was finally discharged on April 16th.

Case 2

Case 2, a 67-year old Swiss male spending his vacation in Italy, had been hospitalised in Calabria from the 17th to 19th of February because of bilateral pneumonia. Antibiotic therapy with ampicillin/sulbactam and levofloxacin was initiated. On February 19th, the patient was transferred to our MICU.

Upon arrival at our hospital, antibiotic therapy was changed to piperacillin/tazobactam and clarithomycin. Because of worsening of the respiratory situation, extracorporeal membrane oxygenation (ECMO) was installed. A multiplex-PCR of the BAL was positive for Influenza A and therapy with oseltamivir was started. The patient was not put on droplet isolation because he was mechanically ventilated at that time. Piperacillin/tazobactam was switched to imipenem. The cardiopulmonary situation slowly improved and the ECMO could be removed on March 14th. Because of an inguinal deep vein thrombosis and at the same time bleeding complications in the nasopharynx, an inferior V. cava (IVC) filter was installed. Because of recurrent fever all intravascular catheters were exchanged on March 15th and cultures of the central catheter tip showed KPC-KP. The same microorganism could be detected in a BAL performed on March 17th because of respiratory deterioration. Antibiotic therapy was switched to meropenem, colistin and tigecycline assuming ventilator-associated pneumonia. The patient recovered and could finally be extubated on April 7th. After removal of the IVC filter, the patient was transferred to another hospital on April 15th.

Case 3

Case 3, a 39-year old man, was initially admitted to a hospital in Austria because of sepsis and bilateral pneumonia on March 9th. Due to respiratory deterioration of the intubated patient, ECMO was installed and the patient was transferred to our MICU.

Influenza B and *S. aureus* could be isolated from the patient's sputum and therapy with oseltamivir and amoxicillin/clavulanate was begun. Due to the Pantone-Valentine-Leukocidine-(PVL)-producing *S. aureus*, clindamycin (for 14 days) and intravenous immunglobulins (for 3 days) were administered. No droplet isolation was installed because the patient was on mechanical ventilation. The patient remained under ECMO until March 24th. He exhibited multiple complications of sepsis: because of acral necrosis due to microvascular derangements, both feet and 9 fingers had to be amputated in the course of hospitalisation. Short-term agranulocytosis was probably related to severe sepsis (including PVL) and/or multiple medications. Furthermore, the patient developed renal failure and was dependent on renal replacement therapy until transferal. In the patient screening from March 21th, swab samples of the patient's skin, pharynx and rectum were positive for KPC-KP. Antibiotic therapy was first switched to meropenem. Tigecyclin and colistin were added on March 26th due to suspected VAP with secondary KPC-KP bacteremia. The patient could finally be extubated and was transferred to another hospital on April 23th.

Discussion

Outbreak and epidemiology

To the best of our knowledge this is the first published outbreak with KPC-KP in Switzerland confirmed by PFGE-identical strains.

We postulate case 2, who was transferred from an Italian hospital, being the index patient of the described outbreak. This hypothesis is corroborated by looking at the epidemiology of KPC-KP in Europe. Italy is one of the few European countries where CRE are considered to be endemic, especially KPC-2 and KPC-3 producing *K. pneumonia* [1,4,5]. Many cases and outbreaks of CRE in other countries have been attributed to patient transfers from Italy [6,9].

Case 3 was admitted to the ICU after first isolation of the bacterium and is therefore excluded as possible source of the outbreak. Case 1 was not hospitalised abroad within the 12 months preceding the outbreak, which makes him less likely to be the index patient.

Infection control measures

Since the gastrointestinal tract is the most common human reservoir, KPC-KP acquisition by ingestion is likely [17]. Depending on the gastrointestinal flora and antibiotic consumption, gastrointestinal colonisation is transient or permanent. During the time of gastrointestinal carriage, shedding and transmission to other patients is possible [17]. Even though this mechanism may account for transmission in the community setting, transmission of KPC-KP in western countries is almost exclusively seen in hospitals [17]. Although never proven in health care settings, transmission is assumed to happen through contact between patients and personnel.

Fortunately, our outbreak was rapidly controlled with rigorous hand hygiene, contact precautions with cohorting and surface disinfection. However, screening of exposed patients was incomplete and follow-up of discharged patients was difficult. One sixth of the patients at risk were not screened because of early discharge to another institution. They could potentially serve as reservoir for KPC-KP and spread the bacteria within the community or within health care institutions in case of rehospitalisation. Electronic patient labelling might help to identify these patients in case of readmission to our institution. Admission to other institutions however would go undetected as electronic patient systems are not connected between different hospitals in our region. Having organisational problems in the regional setting shows how complicated it may be to obtain and provide information about outbreaks and local epidemiology on an international level. Therefore better regional, national and international collaboration is needed as already proposed by the ESCMID Expert Group on acquired carbapenemases 2010 [18].

Given the absence of KPC-KP in our institution before this outbreak, our laboratory was not prepared to do patient screenings for KPC-KP. Therefore screenings during the outbreak were done without selective culture media for KPC-KP, resulting in a lower screening sensitivity. After control of the outbreak, a screening program for patients at risk for CRE has been implemented in our institution using selective culture media. Up to date, KPC-KP has not been detected in our hospital since the outbreak, neither in clinical nor in screening samples. In light of our experiences, we recommend initiation of appropriate screening methods for CRE in every hospital.

Clinical aspects

All of our patients exhibited risk factors for the acquisition of *K. pneumonia*. Whereas case 1 was immunocompromised due to high dose chemotherapy, all three patients suffered of severe infections and were therefore treated with broad-spectrum antibiotics before infection with KPC-KP. In addition, cases 2 and 3 had severe sepsis, being itself a state of immunosuppression [19], and had a prolonged ICU stay. Moreover, these two patients were on ECMO and on mechanical ventilation at time of KPC-KP isolation, both factors contributing to the increased susceptibility to nosocomial pathogens [20].

Data on treatment of CRE are scarce. As has been shown in vitro, carbapenems seem to have a synergistic effect given together with colistin or tigecycline despite the presence of carbapenemase [21,22]. Our patients were treated with a combination therapy consisting of meropenem, tigecycline and colistin. In a retrospective study analysing 125 cases of bloodstream infections (BSI) with KPC producing bacteria, this combination therapy was associated with a decreased mortality (34 vs 54%) compared to patients with monotherapy [23]. Similar results have been published by others [24,25]. In addition, development of resistance has been documented under monotherapy, especially for colistin [26]. Combination therapy against KPC-KP should therefore be the treatment of choice until further data based on prospective randomized trials are available.

Conclusion

Our report describes a KPC-2 outbreak in Switzerland following a patient transfer from Italy and its containment by application of rigorous infection control measures.

Infections in the three affected individuals were successfully treated with a triple therapy consisting of meropenem, colistin and tigecycline.

Ethical approval

No formal informed consent was obtained from patients as the evaluation was considered within the overall quality control system instituted at the hospital.

Acknowledgements

There was no financial support or writing assistance and there is no potential conflict of interest for any of the contributing authors.

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Figures

Fig. 1 Timeline of the outbreak

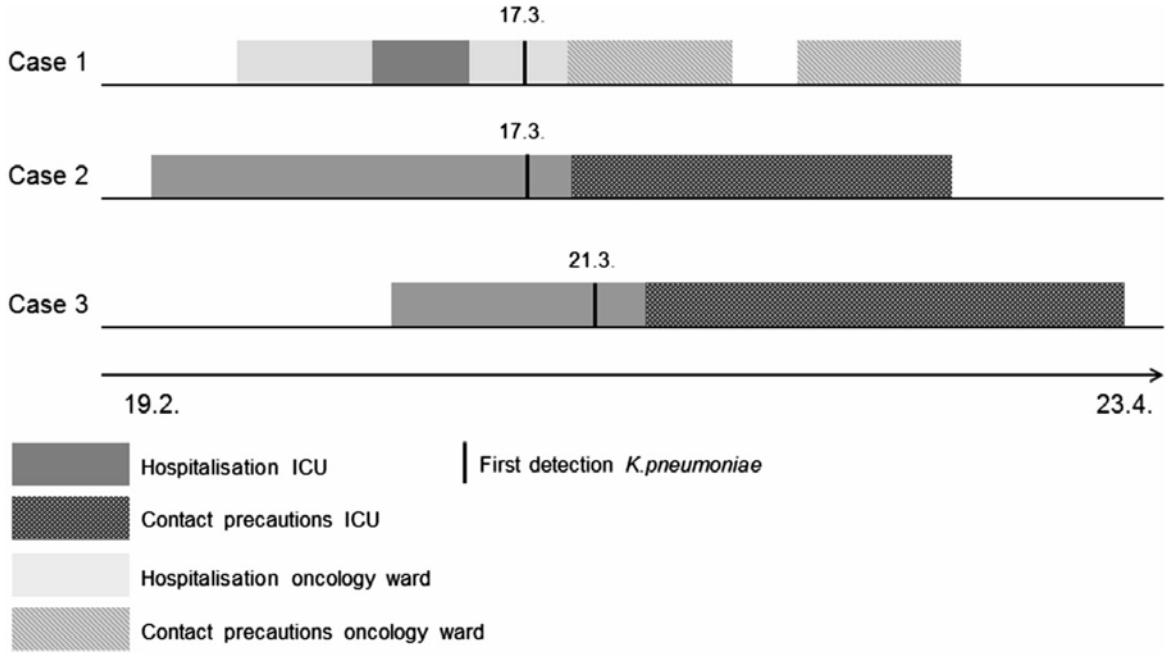
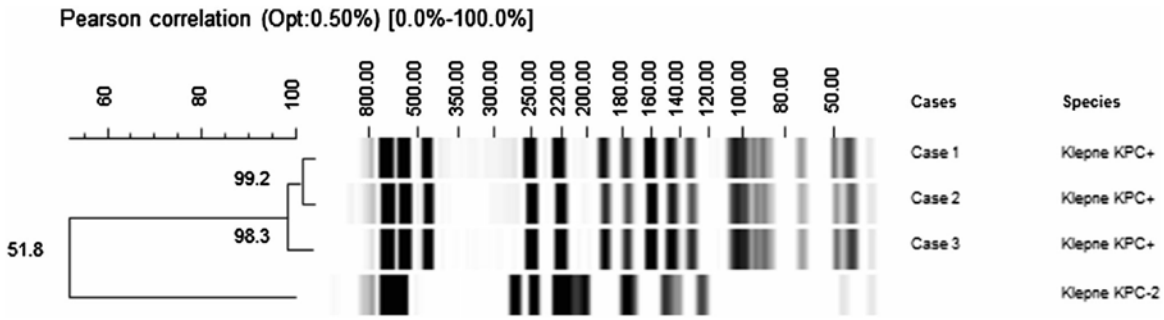


Fig. 2 Pulsed-field gel electrophoresis (PFGE) using *Xba*I of the three KPC-2 *K. pneumoniae* isolates compared with an unrelated KPC-2 *K. pneumoniae* strain



Tables

Table 1: Outbreak of KPC-KP, February to April 2013: Characteristics of involved patients (n=3), all having been treated with meropenem, colistin and tigecyclin

Case	Underlying condition	Reason for MICU-admission	Hospita-lisation abroad[1]	Device[2]	KPC-KP positive samples	KPC-KP infection	Duration of antibiotic treatment	Survival [3]
1	Multiple myeloma, high dose chemotherapy	Aplasia and bilateral pneumonia (no microorganism)	no	CL	Blood, BAL	CRBSI assumed, HAP	12 days	yes
2	None	Bilateral pneumonia (Influenza A)	Italy	ECMO, MV, IVC filter, CL	Tracheo-bronchial, CL[4]	VAP	4 weeks	yes
3	None	Bilateral pneumonia (Influenza B, MSSA)	Austria	ECMO, MV, cvvHD, CL	Skin, pharynx, rectum, blood, BAL	VAP with secondary BSI assumed	4 weeks	yes

MICU=medical intensive care unit, KPC-KP=KPC-producing *Klebsiella pneumoniae,* CL=central line, CRBSI=catheter-related blood stream infection, HAP=hospital acquired pneumonia, BAL=bronchoalveolar lavage, ECMO=extracorporal membrane oxygenation, MV=mechanical ventilation, IVC=inferior vena cava, VAP=ventilator associated pneumonia, MSSA=methicillin sensitive *Staphylococcus aureus*, cvvHDF=continuous veno-venous hemofiltration, BSI=blood stream infection

[1] within 30 days before MICU admission, [2] at time of KPC-KP detection, [3] at 30 days after KPC-KP detection, [4] i.e. cultured catheter tip